A comprehensive analysis of vascular complications in 3,889 glioma patients from the German Glioma Network

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Abstract: Ischemic strokes, intracranial hemorrhages (ICH) and deep venous thromboembolism (DVT) are clinically important events in patients with gliomas. In this multicentre, noninterventional observational study, current data pertaining to frequency, contributing factors and outcomes of vascular events during times of anti-angiogenic therapy with the antibody against vascular endothelial growth factor, bevacizumab (BEV) was collected from the German Glioma Network. Among 3,889 glioma patients, 70 ischemic strokes (1.8 %) and 123 ICH (3.2 %) were recorded. 143 DVT (5.0 %) were recorded in 2,855 patients. Rates of DVT and ICH, but not of ischemic strokes, increased with the World Health Organization (WHO) grade of glioma. In 81 BEV-treated patients, five ischemic strokes (6.2 %), one ICH (1.2 %) and six DVT (7.4 %) were documented. Compared to patients that were not treated with BEV, ischemic stroke rate was significantly higher during treatment with BEV ($p < 0.001$). The rates of DVT ($p = 0.123$) or ICH ($p = 0.571$) in BEV-treated patients did not differ. On cerebral magnetic resonance imaging (MRI), BEV-related ischemic strokes appeared as diffusion-restricted sites next to contrast-enhancing tumor. 67 % of ICH, 61 % of ischemic strokes and 18 % of DVT occurred postoperatively (within 30 days after tumor resection). Outcome after postoperative ICH was significantly worse than after spontaneous ICH ($p = 0.008$). Ischemic stroke outcomes did not differ between postoperative and spontaneous occurrence ($p = 0.401$). Rate of pulmonary embolism did not differ significantly between postoperative and spontaneous DVT ($p = 0.133$). Relatively low rates of ICH and DVT might be partially due to a high proportion of low-grade gliomas in this patient cohort. The finding of a relevant number of symptomatic, therapy-associated intracerebral diffusion restrictions should be controlled in ongoing phase III studies.

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Vascular complications in a GGN cohort of 3889 patients

Key words

Deep venous thrombosis, intracranial hemorrhage, stroke, glioma, bevacizumab

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Abstract

Background: Ischemic strokes, intracranial hemorrhages (ICH) and deep venous thromboembolism (DVT) are clinically important events in patients with gliomas.

Methods: In this multicentre non-interventional observational study current data about frequency, contributing factors and outcomes of vascular events in times of anti-angiogenic therapy with the antibody against vascular endothelial growth factor, bevacizumab (BEV) was collected in the German Glioma Network (GGN).

Results: Among 3889 glioma patients 70 ischemic strokes (1.8%) and 123 ICH (3.2%) were recorded. 143 DVT (5.0%) were recorded in 2855 patients. Rates of DVT and ICH but not of ischemic strokes increased with the WHO grade of glioma.

In 81 BEV-treated patients 5 ischemic strokes (6.2%), 1 ICH (1.2%) and 6 DVT (7.4%) were documented. Compared to patients that were not treated with BEV, ischemic stroke rate was significantly higher during treatment with BEV ($p<0.001$). The rates of DVT ($p=0.123$) or ICH ($p=0.571$) in BEV-treated patients did not differ. On cerebral MRI BEV-related ischemic strokes appeared as diffusion-restricted sites next to contrast-enhancing tumor.

67% of ICH, 61% of ischemic strokes and 18% of DVT occurred postoperatively (within 30 days after tumor resection). Outcome after postoperative ICH was significantly worse than that after spontaneous ICH ($p=0.008$). Ischemic stroke outcomes did not differ between post-operative and spontaneous occurrence ($p=0.401$). Rate of pulmonary embolism did not significantly differ between post-operative and spontaneous DVT ($p=0.133$).

Discussion: Relatively low rates of ICH and DVT might be partially due to a high proportion of low-grade gliomas in this patient cohort. The finding of a relevant number of symptomatic, therapy associated intracerebral diffusion restrictions should be controlled in ongoing phase III studies.

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Introduction

Ischemic strokes, intracranial hemorrhages (ICH) and deep venous thromboembolism (DVT) are

frequent in patients with glioma [13], [22-24].

Consequences may be severe and result in deteriorating quality of life and increasing disability. It is assumed that ICH and ischemic strokes [13] are particularly associated with a dismal prognosis. Current data about frequency, causes and outcomes of vascular events appear crucial for treating physicians, particularly in times of anti-angiogenic therapies and their possible side effects.

Primary objective of this multicentre non-interventional observational study was a comprehensive analysis of spontaneous and postsurgical vascular complications in glioma patients with a special focus on the effect of anti-angiogenic therapy with the antibody against vascular endothelial growth factor (VEGF), bevacizumab (BEV).

Methods

Data collection

Clinical data about ischemic strokes, ICH and DVT in glioma patients (n=3889) have been collected in the German Glioma Network (GGN). The GGN is a multicentric (Bochum, Bonn, Düsseldorf, Dresden, Freiburg, Hamburg, Heidelberg, München, Tübingen) prospective cohort study that enrolled newly diagnosed patients with various types of glioma and frozen tissue asservation from October 2004 to October 2010. In addition to the clinical centres there are several reference centres for collection and analysis of clinical, pathological and molecular parameters of glioma. The patients were not commonly enrolled into clinical trials, and treatment decisions were made by the treating physicians, patients and their families, without awareness of results of molecular parameters. Progression was defined locally according to Macdonald criteria and not centrally reviewed. All patients gave written informed consent. All activities of the GGN have been approved by the review boards of the participating institutions. Within the GGN, patients are prospectively followed by standardized clinical and MRI examinations. Data are documented on CRF and centrally stored and monitored as outlined before (http://www.gliomnetzwerk.de) [28]. The GGN did not intend interventions. The GGN established an observational cohort with standard

operating procedures for follow up and data acquisition at all levels.

Between October 2004 and January 2010 data about 3889 patients have been recorded in a central database. The clinical centres have centrally recorded vascular complications. The individual centers redorded numerous other patient data (age, glioma type, date of resection, adjuvant therapies, event related death) on dedicated case record forms for central data storage in addition to the basic event data (type and date of event). For completion and amendment of centrally documented data additional chart information (clinical outcome, concomitant medication, vascular risk factors) have been collected from the centres in 2010 by C.S..

Determination of event rate

From 3889 patients included between 2004 and 2010 in the GGN rates of ischemic strokes and ICH were determined. The DVT rate was calculated from 2855 patients since two clinical centres did not document DVT. Occurrence within thirty days after surgery was classified as postoperative. Additionally, event rates were calculated for the most frequent glioma types.

Determination of event rate under BEV-treatment and characterisation of events

Within the GGN patient population 81 patients were treated with BEV. Events were regarded as BEV-related when they happened during or max. 4 weeks after BEV-therapy.

The number of events within 81 patients that were treated with BEV was compared with the number of not postoperative events among 3808 patients that were never been treated with BEV. Detailed clinical information and MRI images from BEV-related ischemic strokes were collected from the clinical centres.

Comparison of postoperative and non-postoperative events

All vascular complications were analysed separately according to postoperative or non-postoperative occurrence.

For ischemic strokes the following characteristics were looked at and compared between the two groups: patient age, tumor histology, clinical outcome, cerebrovascular risk factors (arterial hypertension, diabetes mellitus, atrial fibrillation, persisting foramen ovale) and associated therapy. Clinical outcome was determined from clinical data by retrospective estimation of modified rankin score (MRS) after the event. This approach has been used before [13] and gives an approximation of severity of stroke. It does not take into account the MRS before stroke.

For ICH patient age, tumor histology, hemorrhage type (intracerebral, subdural, epidural, subarachnoidal), clinical outcome (with retrospective modified rankin score) and bleeding risk factors (arterial hypertension, thrombocytopenia, use of anticoagulants or aspirine) were determined and compared.

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Accordingly, for DVT patient age, tumor histology, clinical outcome (pulmonary embolism, event related death), concomitant therapies and use of steroids were looked at.

Statistics

Categorical data were compared using Fisher's exact or chi-square test. Mann-Whitney-U-test was used to analyze age and steroid dose. P-values <0.05 were considered as statistically significant. To control the familywise error rate the Holm-Bonferroni Method was applied. Statistical analysis were performed using IBM SPPSS V.20 .

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Results

Event rate in the GGN patient population and relation to tumor histologies

Among 3889 patients 70 ischemic strokes (1.8%) determined clinically and radiographically and 123 ICH (3.2%) as single events in individual patients, except for one patient with two ischemic events, were documented. In addition, 143 DVT (5.0%) were recorded in 2855 patients. Distribution of the most frequent gliomas is shown in Table 1. Event rates related to the glioma type and WHO grade, namely WHO grade I: pilocytic astrocytoma (PA), WHO grade II: diffuse

astrocytoma (AII), oligoastrocytoma (OAII) oligodendroglioma (ODII), WHO grade III: (anaplastic) astrocytoma (AA), oligoastrocytoma (AOA), anaplastic oligodendroglioma (AO) and glioblastoma (GB) of WHO grade IV are depicted in Table 2.

The ischemic stroke rate did not differ between tumor entities (p=0.383), whereas ICH rates increased significantly with degree of malignancy (p<0.001). Similarly, there was a significant correlation between WHO grade and the frequency of DVT (Table 2, p<0.001). Interestingly, in case of non-postoperative events this correlation between the WHO grade and frequency of vascular events was only seen for DVT (p<0.001, data not shown).

Rate and characterization of BEV-associated vascular events

During or maximal four weeks after BEV therapy 6 DVT (7.4%), 1 ICH (1.2%) and 5 ischemic strokes (6.2%) in the group of BEV-treated patients (n=81) were documented (Table 3). One patient suffered from two ischemic events within eight weeks.

Among the patients that were never treated with BEV (n=3801) 100 DVT (3.6%), 39 ICH (1.0%) and 22 ischemic strokes (0.6%) were registered as non-postoperative events.

In comparison, ICH rates were similar (1.2% vs. 1.0%, p=0.571). The rate of DVT showed a trend for higher frequency under BEV (7.2% vs. 3.6%, p=0.123). Ischemic strokes were more frequent during treatment with BEV (6.2% vs. 0.6%, p<0.001).

As these data indicate a higher frequency of ischemic strokes in patients treated with BEV compared with patients never treated with this drug, more detailed clinical data and MRI images were analyzed from the 4 affected patients.

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All ischemic strokes were situated on the side of the tumor, either in deep white matter, basal ganglia or thalamus, all patients had been treated with radiotherapy during the course of disease. Median patient age was 63 (59-69), median MRS after the event was 3 (3-6). One patient died shortly after the event. Two of four patients showed vascular risk factors. In all patients partial

response to BEV was diagnosed.

In the analysis of the 3/5 available MRI scans lacunary rather than territory diffusion-restricted areas in proximity to residual contrast enhancement were visible (Table 4 and Fig. 1).

Comparisons between postoperative and non-postoperative events in the GGN patient population

Ischemic strokes (Table 5)

43/70 (61%) occurred postoperatively and 27/70 (39%) without relation to surgery. Patient age was lower in the group of patients with postoperative events than in non-postoperative events (53 years vs. 61 years, p=0.098). Tumor entities were distributed without difference (p=0.582). The rate of severe disability did not differ between postoperative and non-postoperative brain infarctions (MRS > 3: 71 % vs. 59 %, p=0.401). Patients with postoperative brain infarctions showed a significantly lower rate of cerebrovascular risk factors (38 % with at least one risk factor) than patients with non-postoperative events (73% with at least one risk factor, p=0.014). In 14 of 27 (52%) patients with non-postoperative ischemic strokes radiotherapy to the involved part of the brain was part of the treatment a median of 1.5 years before the event. In all these patients ischemic stroke pattern did not seem cardiogenic. 8/14 patients did not show any cardiovascular risk factors. In 1 of 14 patients an intracranial arterial stenosis was documented.

Intracranial hemorrhages (Table 6)

Of all ICH, 68% (83/123) occurred within 7 days after tumor resection, whereas 32% (40/123) occurred without close timely relation to surgery. Distribution of glioma type showed more grade III tumors (30% vs. 9%) in the non-postoperative ICH. Particularly, tumors with oligodendroglial and oligoastrocytic histology showed more often non-postoperative than postoperative bleeding (13% vs. 1%).

Types of ICH differed significantly in their distribution between postoperative and non-postoperative events (p=0.002). Intraparenchymal bleeding was recorded about equally often (71%

vs. 75%), whereas epidural hematoma occurred more often postoperatively (17% vs. 0%). Subdural (20% vs. 11%) und subarachnoidal hematomas (5% vs. 0%) were more often recorded non-postoperatively. Severe disability was registered more often in postoperative bleeding (MRS > 3: 49% vs. 21%, p=0.008), but other confounding factors like a surgery-related neurological deficit cannot be excluded to contribute to this.

Risk factors for ICH were documented in 35% of cases in postoperative ICH and in 32% of non-postoperative ICH (p=0.779).

Deep venous thromboembolism (Table 7)

DVT occurred in 23/130 (18%) of the events within 7 days after tumor resection and in 50/130 (38%) within 4 weeks after tumor surgery.

In the group of non-postoperative DVT patients were of older median age (59 ys vs. 51 ys, p=0.018). Glioma types were distributed without difference in the two groups (p=0.623). Median steroid dose was not different between the two groups (median 1 mg vs. 2 mg, p=0.622).

Non-postoperative DVT were diagnosed in 22/106 (22%) during running radio-(chemo-)therapy, 15% during chemotherapy with temozolomide, 10% during therapy with nitrosourea, and 6% during therapy with BEV. The proportion of severe DVT with pulmonary embolism was lower in non-postoperative events (40% vs. 56%) without reaching statistical significance (p=0.133).

Discussion

The present non-interventional observation study provides relevant information on the frequency of the main vascular events in a carefully prospectively documented relevant cohort of patients with gliomas. As the participating centers included patients based on the availability of biomaterial from the surgery, this analysis provides a clear overview on the natural course of development of vascular complications in gliomas. Limitations of the present data are the only cursory monitorings that have been done on original chart data and that numbers in the GGN cohort not necessarily reflect the

global incidence of glioma subgroups, as the GGN has certain priority topics in low-grade and anaplastic gliomas. In our cohort the rate of GB/malignant glioma was lower than in the Central Brain Tumor Registry of the United States (CBTRUS; GGN: 46,3% vs. CBTRUS: 61,0%). The rate of grade III and II astrocytoma and oligodendroglioma was with 39.6% much higher in our cohort than in CBTRUS (23.7%). The rates of PA (GGN: 3.0%, CBTRUS 5.2%) and of others/unknown (GGN: 11.1%, CBTRUS 10.1%) were similar [1].

Ischemic strokes

Data about the frequency of brain infarction in patients with glioma are rare. In a retrospective review of Kreisl *et. al* [13], in which glioma (60%) and other tumor types such as meningioma and CNS-Lymphoma were included minimum ischemic stroke rate was 1.3% in a population of 5,100 patients. In our study, which is the first only focussing on gliomas, the rate of brain infarction is 70/3889 patients (1.8%) and therefore in the same range. Here, there were no differences according to WHO grade.

Most ischemic strokes (61%) occurred postoperatively and less often the common cerebrovascular risk factors could be detected than in non-postoperative strokes. This observation of a relevant incidence of postoperative ischemic lesions, often explaining an otherwise unexplainable worsening had been thoroughly followed with DWI studies in the past [29]. Outcome of postoperative versus non-surgery-related ischemias was not different. With anti-angiogenic BEV therapy more ischemic strokes were documented than without that therapy (6.1 versus 0.6%). This appears surprising, as this was not observed in other studies with glioma [7] (ischemic stroke rate: 1.9%, no control group) or in side effect monitoring in other extra-cranial tumor entities [18], [26]. On the other hand intracerebral diffusion-restricted sites in glioma are well appreciated to occur with BEV-therapy [19], [9]. The origin and nature of these diffusion-restricted areas are controversially discussed, therapy-associated hypoxic areas in proximity of the tumor [20] or cell dense tumor areas due to altered tumor growth [17] could be relevant causes. In our MRI analysis diffusion-restriction was

confined to lacunar areas in proximity of tumors, while contrast enhancement in the remaining tumor was decreasing. This allows for both or an overlap of both explanations.

The high rate of BEV-induced diffusion-restricted sites in glioma patients points to a growth-related specific effect in this tumor entity. These diffusion-restrictions can be associated with neurologic deterioration and should not be seen as harmless side effects, although there might be a relevant number of non-reported asymptomatic cases. In the work of Rieger et al. [19] 13 (72%) of 18 analysed patients showed diffusion-restricted sites. The diffusion-restricted areas may even predate contrast enhancing tumor progression, e.g. in more than 80% of cases reported by Gupta et al. [9], and thus might be nothing but another correlate of progressive disease.

Eventually, a diffusion-restriction next to the tumor under therapy with BEV with neurological worsening may in most cases may be no „classic“ ischemic stroke due to thrombotic or embolic vessel occlusion but rather a local effect of therapy. It would not be justified to assume an elevated risk of macroangiopathic or embolic stroke under BEV-therapy. The exact risk for diffusion-restriction with neurologic worsening should be determined in the context of the ongoing phase III trials (e.g. Avaglio, NCT00943826, [21]).

Intracranial hemorrhage

The frequency of non-postoperative ICH in glioma varies from 2-25% in the literature [10], [22], [27]. The postoperative risk for ICH is about 2-5% [6], [23].

In our study ICH was registered in 3.2% of all patients, two thirds of events occurred within 7 days after surgery.

Overall, there was an increase of bleeding rate with WHO-grade of the glioma. It remains unclear from our data, if this is an effect of a higher number of resections in malignant gliomas. Among anaplastic tumors a relevant number of non-postoperative ICH occurred in tumors with oligondendroglial or oligoastrocytic differentiation. This might reflect the fact that in these tumors a tendency for spontaneous bleeding is known [14].

Among non-postoperative ICH subdural hemorrhages were more frequent. The latter and the fact that many non-postoperative ICH start intratumorally without initial major neurologic deficit might explain the observed better outcome of spontaneous bleedings.

Interestingly, only in about one third of cases in postoperative and non-postoperative ICH bleeding risk factors were reported. This supports the fact that the majority of non-postoperative hemorrhage indeed arise „spontaneously“ due to fragile tumor blood vessels.

With BEV-therapy among 81 patients only one ICH (according to a rate of 1.2%) was observed, which gives a similar rate of non-postoperative hematoma as in patients that have never been treated with BEV (1.0%) and does not support an elevated risk of ICH during BEV therapy, with the limitation of the small number of patients observed in our study.

Comparable results were observed by Friedman *et al.* (ICH-rate under BEV 2,4%, with irinotecan 3.8%, no control group) *[8]*. In BEV-treated patients with primary extracranial tumors an ICH rate of 3.7% [12] and of 1-2% in patients with intracerebral metastases [2] was not significantly elevated.

Deep venous thromboembolism

Data about DVT show an extensively varying probability of 4-30% to develop DVT during course of glioma disease [15], [3], [5], [25], [24]. Generally, large studies with some thousand patients show smaller rates than small prospective studies with less than hundred patients. Our rate of 143 events in 2855 patients (5%) is in the low range.

A correlation between the rate of DVT and the WHO Grade of glioma has been observed before [15], [3]. This may not only reflect a higher degree of disability in patients, more intensive concomitant therapies or increasing steroid dose, but may be a specific prothrombotic, paraneoplastic effect of malignant gliomas [11].

A high rate of DVT has also been found in studies with BEV in malignant glioma (1.6%-12.5%, discussed in [4]). Larger comparing analyses with BEV-naive control groups only exist for other

tumor entities and showed a moderately increased relative risk for DVT of 1.33 [16]. Facing the *per se* very high DVT risk in malignant glioma compared to other tumor entities, our result of only a trend to a higher DVT rate under BEV indicates that the specificity of this risk for BEV treatments in glioblastoma may have been overestimated. Nonetheless, interpretation is weakened by the low number of BEV treated patients in our cohort.

The comparison of postoperative and non-postoperative DVT did not show significant differences of outcome and other parameters. Patients with non-postoperative DVT were older, which might support the fact that age in itself is a risk factor for DVT [24].

Summary

This study shows current rates and characteristics of vascular complications in patients with glioma. Compared to earlier studies relatively low rates of ICH and DVT were reported, which might be due to a high proportion of low-grade gliomas in our patient cohort.

Under the therapy with BEV symptomatic, therapy associated intracerebral diffusion restrictions were seen in a relevant amount of cases.

There was a trend for a higher DVT rate under therapy with BEV. No difference appeared in the frequency of ICH. These findings should with respect to our small event numbers in the BEV group be controlled in the ongoing phase III studies.

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Table 1: Characteristics of GGN patient population and number of vascular events

	GGN patients (N=3889)
Glioma type - GB - AA/AOA/AOD - AII/ODII/OAII - PA - other/unknown	 1800 (46.3%) 646 (16.6%) 896 (23.0%) 115 (3.0%) 432 (11.1%)
Ischemic strokes, N (%)	70 (1.8%)
ICH, N (%)	123 (3.2%)
DVT[a], N (%)	143 (5.0%)

Abbreviations: (A)A: (anaplastic) astrocytoma; (A)OA: (anaplastic) oligoastrocytoma; (A)OD: (anaplastic) oligodendroglioma; DVT: deep venous thrombosis; ICB: intracranial bleeding; GB: glioblastoma; PA: pilocytic astrocytoma

[a] of 2855 patients

Table 2: Distribution of vascular events according to glioma type

Event	Glioma type			p-value
	AII/OAII/ODII	AA/AOA/AO	GB	
Ischemic stroke, N (%)	13/896 (1.5%)	14/646 (2.2%)	40/1800 (2.2%)	0.383
ICH, N (%)	13/896 (1.5%)	20/646 (3.1%)	88/1800 (4.9%)	<0.001
DVT, N (%)	13/653 (2.0%)	18/471 (3.8%)	98/1361 (7.2%)	<0.001

Abbreviations: (A)A: (anaplastic) astrocytoma; (A)OA: (anaplastic) oligoastrocytoma; (A)OD: (anaplastic) oligodendroglioma; DVT: deep venous thrombosis; ICB: intracranial bleeding; GB: glioblastoma

Table 3: Number of non-postoperative vascular events and distribution of glioma type among patients with BEV treatment and patients never been treated with BEV

	Non BEV-treated (N=3808)	BEV-treated (N=81)	p-value
Ischemic strokes, N (%)	22 (0.6%)	5 (6.1%)	<0.001
ICH, N (%)	39 (1.0%)	1 (1.2%)	0.571
DVT, N (%)	100 (3.6%) [a]	6 (7.4%)	0.123
Glioma type - GB - AA/AOA/AO - AII/OAII/ODII - PA - Other/unkown	 1742 (45.7%) 633 (16.6%) 891 (23.4%) 405 (10.6%) 137 (3.6%)	 58 (71.6%) 13 (16.0%) 5 (6.2%) 0 (0%) 5 (6.2%)	 <0.001

Abbreviations: (A)A: (anaplastic) astrocytoma; (A)OA: (anaplastic) oligoastrocytoma; (A)OD: (anaplastic) oligodendroglioma; BEV: bevacizumab; DVT: deep venous thrombosis; ICB: intracranial bleeding; GB: glioblastoma

[a] of 2774 patients

Table 4: Characteristics of BEV-associated ischemic strokes

Nr	Age [years]	Localisation of diffusion-restriction	Next to contrast enhancing tumor	Glioma type	Risk factors	MRS (after event)	R to BEV at time of event
1	67	Paraventricular white matter, basal ganglia	Yes	OAIII	None	5	PR
2	63	Paraventricular white matter, basal ganglia	Yes	GB	None	3	PR
3	63[a]	Paraventricular white matter	MRI NA	GB	None	6	PR
4	59	Thalamus, mesial temporal lobe	Yes	GB	AH, Plaques ACI, infiltration of MCA	3	PR
5	69	Thalamus	MRI NA	GB	ACC-Plaque	3	PR

Abbreviations: ACC: Common cerebral artery, ACI: Internal carotid artery, AH: Arterial hypertension, CE: contrast enhancement, DR: diffusion-restriction, MCA: Median cerebral artery, MRI: magnetic resonance imaging, MRS: modified rankin score, NA: not available; Nr: number; PR: partial response, R: response, RT: radiotherapy

[a] second event of patient with event Nr 2

Table 5: Characteristics of patients with ischemic strokes

	N=70		
	Postoperative (N=43)	Non-postoperative (N=27)	p-value
Age [years], Median (Range)	53 (25-78)	61 (39-84)	0.098
Glioma type GB AA/AOA/AO AII/OAII/ODII Other	 26/43 (61%) 8/43 (19%) 7/43 (16%) 2/43 (5%)	 14/27 (52%) 6/27 (22%) 7/27 (26%) 0/27 (0%)	 0.582
Outcome MRS ≤ 3 MRS > 3 of which MRS = 6	 10/34 (29%) 24/3 (71%) 5/34 (15%)	 9/22 (41%) 3/22 (59%) 1/22 (5%)	 0.401
Risk factor None Arterial hypertension Diabetes mellitus Persisting foramen ovale Other (incl. AF)	 18/29 (62%) 8/29 (28%) 0/29 (0%) 0/29 (0%) 3/29 (10%)	 6/22 (27%) 5/22 (23%) 3/22 (14%) 3/22 (14%) 5/22 (23%)	 0.014

Abbreviations: : (A)A: (anaplastic) astrocytoma; (A)OA: (anaplastic) oligoastrocytoma; (A)OD: (anaplastic) oligodendroglioma; AF: atrial fibrillation; GB: glioblastoma; MRS modified Rankin score

Table 6: Characteristics of patients with intracranial bleeding

	N=123		
	Postoperative (N=83)	Non-postoperative (N=40)	p-value
Age [years], Median (Range)	59 (18-85)	54 (27-85)	0.867
Glioma type			
GB	64/83 (77%)	24/40 (60%)	0.038[a]
AA	7/83 (8%)	7/40 (17%)	
AOA/AO	1/83 (1%)	5/40 (13%)	
AII	9/83 (11%)	2/40 (5%)	
OAII/ODII	0/83 (0%)	2/40 (5%)	
PA	1/83 (1%)	0/82 (0%)	
Ependymoma	1/83 (1%)	0/82 (0%)	
Bleeding type			
Intracerebral	59/83 (71%)	30/40 (75%)	0.002
Epidural	14/83 (17%)	0/40 (0%)	
Subdural	9/83 (11%)	8/40 (20%)	
Subarachnoidal	0/83 (0%)	2/40 (5%)	
Outcome			
MRS ≤ 3	38/75 (51%)	23/29 (79%)	0.008
MRS > 3	37/75 (49%)	6/29 (21%)	
of which			
MRS=6	12/75 (16%)	4/29 (14%)	
Risk factors			
None	35/54 (65%)	15/22 (68%)	0.779
Arterial hypertension	14/54 (26%)	6/22 (27%)	
Thrombocytopenia	3/54 (6%)	1/22 (5%)	
Heparinisation	2/54 (4%)	1/22 (5%)	
Aspirine use	1/54 (2%)	0/22 (0%)	

Abbreviations: : (A)A: (anaplastic) astrocytoma; (A)OA: (anaplastic) oligoastrocytoma; (A)OD: (anaplastic) oligodendroglioma; AF: atrial fibrillation; GB: glioblastoma; MRS modified rankin score; PA: pilocytic astrocytoma

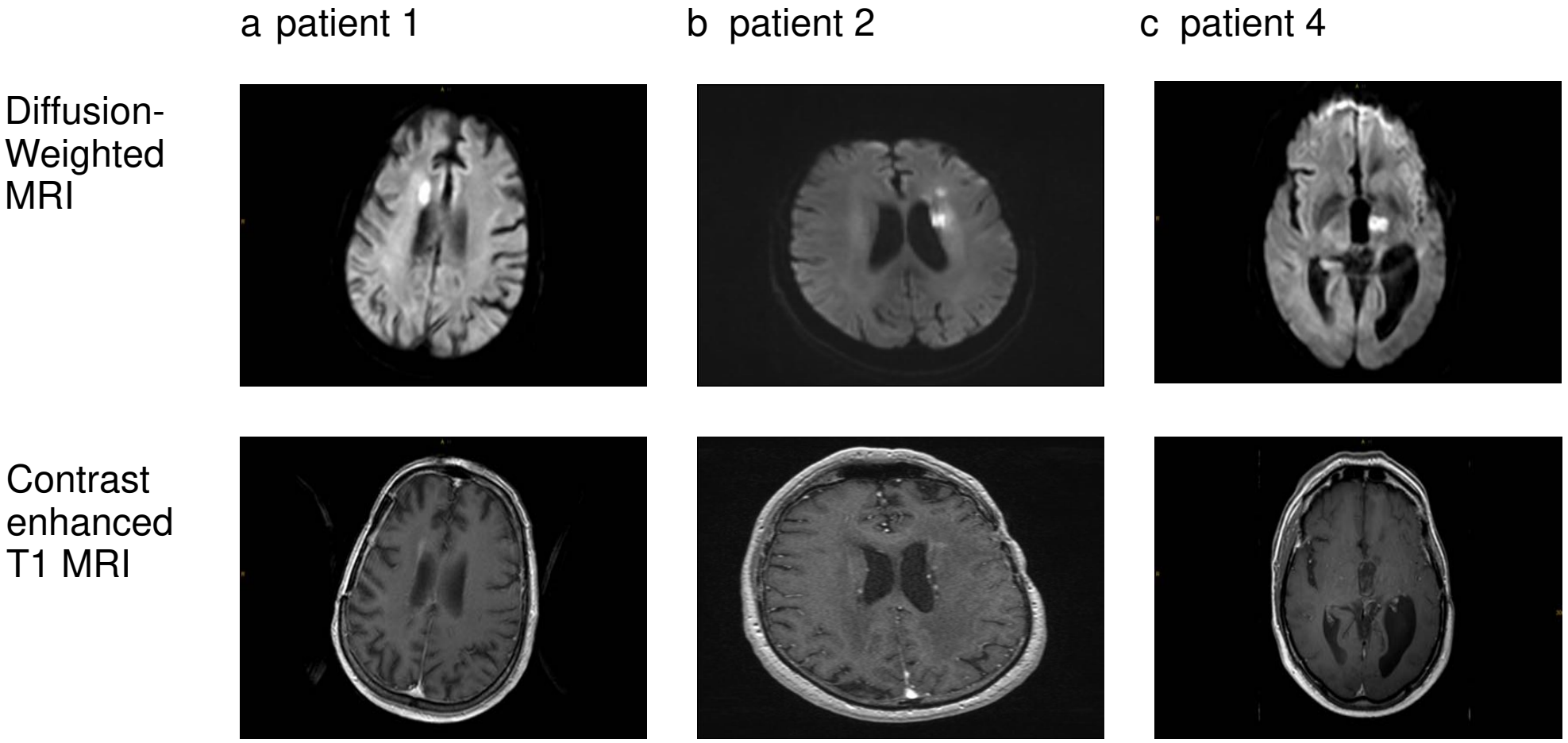
[a]Glioma were grouped according to WHO grade.

Table 7: Characteristics of patients with deep venous thromboembolism

	N= 143; relation to therapy known in 130 cases		
	Postoperative (N=23/130 in 7 days)	Non-postoperative (N=106/130)	p-value
Age [years], Median (Range)	51 (26-78)	59 (24-81)	0.018
Glioma type GB AA/AOA/AO AII/OAII/ODII Other/unknown	 16/23 (70%) 4/23 (17%) 3/23 (13%) 0/23 (0%)	 82/106 (77%) 14/106 (13%) 10/106 (10%) 0/106 (0%)	 0.623
Parallel therapy None Radio(-chemo)therapy Temozolomide Nitrosourea Bevacizumab Other	 22/22 (100%) 0/22 (0%) 0/22 (0%) 0/22 (0%) 0/22 (0%) 0/22 (0%)	 31/89 (35%) 22/89 (25%) 16/89 (18%) 11/89 (12%) 6/89 (7%) 3/89 (3%)	 ND
Steroid use None Steroid dose at patients discharge, median (range)	 3/8 (38%) 1 mg/d (0-16 mg)	 19/42 (45%) 2 mg/d (0-24 mg)	 1.000 0.622
Outcome No pulmonary embolism Pulmonary embolism Pulmonary embolism + death	 10/23 (43%) 13/23 (57%) 1/23 (4%)	 63/104 (61%) 41/104 (49%) 4/104 (4%)	 0.133

Abbreviations: : (A)A: (anaplastic) astrocytoma; (A)OA: (anaplastic) oligoastrocytoma; (A)OD: (anaplastic) oligodendroglioma; GB: glioblastoma; pilocytic astrocytoma: PA; ND Not done

Fig **MRI of ischemic strokes occurring under BEV**



Abbreviations: BVC: bevacizumab, MRI: magnetic resonance imaging, T1: T1 relaxation time